PATENT
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A Process To Improve Or Permit The Oral Absorption Of Polypeptide Drug Substances And Other Poorly Orally Absorbed Drugs While Maintaining Their Pharmacological Effects

Field Of The Invention

This invention, in general relates to prodrugs for the oral administration of therapeutically active polypeptides that are otherwise poorly orally absorbable.

Background Of The Invention

It has been observed in the literature that therapeutically effective olypeptides (aa_n) with two or more amino acids ($n \geq 2$) are poorly absorbed orally. Even a polypeptide of as few as two amino acids, or related structures, exhibits very narrow absorption windows and poor bioavailability. As an example, the Physician's Desk Reference (PDR) reports that the angiotensin converting enzyme (ACE) inhibitor Enalaprilat (R_1-Ala-Pro; $n = 2$) is very poorly absorbed orally. Enalapril (R_2-Ala-Pro), which is a pro-drug of Enalaprilat, is better absorbed orally, but the end result demonstrates only a 25% relative bioavailability of the active moiety (Enalaprilat) released from *in vivo* cleavage of the prodrug. In comparison, Lisinopril (R_3-Lys-Pro) has relatively good solubility in water, but only a moderate oral bioavailability (< 25%), with a T_{max} (time to

maximum serum levels *in vivo*) of more than seven hours. Thus, this class of therapeutic species if preferably administered via a non-oral deliver method, such as by injection. However, even delivered by injection, the therapeutically active species has a relatively short serum half –life.

It is known that some tri-peptides originating in food products may be capable of effective oral absorption, but to an unknown extent. Furthermore, no active tri- or longer peptide drug substances ($n \geq 3$) showing oral absorption have been identified. According to the present invention, it is possible to chemically modify a polypeptide species of known therapeutic utility to both permit the oral administration of the species and to demonstrate effective bioavailability.

Summary Of The Invention

In one embodiment, the present invention provides a prodrug for use in the treatment of physiological conditions comprising a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4 methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl, wherein the carrier moiety is chemically linked to a therapeutic polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally. Preferably, in the prodrug of the invention, *n* is an integer from 3

to 6. More preferably, *n* is 5. In a particularly preferred embodiment, the polypeptide is Tyr-Gly-Gly-Phe-Met.

In an alternative variation, the prodrug of the present invention further comprises a non-therapeutic linker species linking the polypeptide to the carrier species. Preferably, the linker species is an amino acid.

In another embodiment, the present invention contemplates a pharmaceutical composition comprising a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl chemically linked to a therapeutic polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, wherein the polypeptide is poorly absorbed orally, and a pharmaceutically effective adjuvant species.

In yet another embodiment, the present invention provides a method for enhancing the oral availability of therapeutic polypeptides of the general formula formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally, wherein the method comprises the step of chemically linking the polypeptide to a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl to form a prodrug. Preferably, this embodiment of the present invention provides a prodrug where the polypeptide is chemically linked

to the carrier moiety through a non-therapeutic linker species. More preferably, the linker species is an amino acid.

In an alternative embodiment, the invention of the instant application encompasses a method for the treatment of a physiological condition through the oral administration of a therapeutically effective species comprising the steps of chemically linking a therapeutic polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally, to a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5 trimethoxycinnamoyl to form a prodrug, and orally administering the prodrug to a patient exhibiting the physiological condition. Preferably, in the practice of the method of the present invention, the polypeptide is chemically linked to the carrier moiety through a non-therapeutic linker species. More preferably still, the linker species is an amino acid.

In still another embodiment, the invention of the instant application provides for a method for the controlled release administration of a therapeutically effective polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally, comprising the steps of chemically linking the polypeptide to a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-

methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl to form a prodrug, and orally administering the prodrug to a patient. In a preferred embodiment, the polypeptide is chemically linked to the carrier moiety through a non-therapeutic linker species, and, more preferably still, the linker species is an amino acid.

Detailed Description of the Invention

In one embodiment, the present invention provides a prodrug for use in the treatment of physiological conditions comprising a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4 methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl, wherein the carrier moiety is chemically linked to a therapeutic polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally. Preferably, in the prodrug of the invention, *n* is an integer from 3 to 6. More preferably, *n* is 5. In a particularly preferred embodiment, the polypeptide is Tyr-Gly-Gly-Phe-Met.

In an alternative variation, the prodrug of the present invention further comprises a non-therapeutic linker species linking the polypeptide to the carrier species. Preferably, the linker species is an amino acid. Thus, the prodrug of the present invention can be viewed as a three-component entity: the first, therapeutically active component is the polypeptide; the second is the linker

species, possibly an additional, non-therapeutic amino acid; and the third is the carrier moiety.

When delivered orally, the prodrug of the present invention is capable of delivery a systemic dose of the active drugh species to a patient ingesting the prodrug. The active polypeptide, normally degraded in the gastrointestinal tract to non-therapeutic forms, survives and is broken down, probably by enzymatic hydrolysis in the liver. An added benefit of the present invention is that the kinetics of such breakdown to release the active ingredient are significantly slower than that associated with other methods of deliver of the unmodified polypepetide, effectively permitting a controlled relase of the active species into the patient's system.

In another embodiment, the present invention contemplates a pharmaceutical composition comprising a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl chemically linked to a therapeutic polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, wherein the polypeptide is poorly absorbed orally, and a pharmaceutically effective adjuvant species.

As would be recognized by one of skill in the appropriate art area, one or more of the amino acids of the therapeutically active polypeptides used in conjunction with the present invention may be modified chemically or

conformationally without significantly diminishing the pharmacological activity of the therapeutic entity. These modified polypeptides may be used in the practice of the present invention.

Ideally, the prodrug of the present invention is formulated into a pharmaceutical composition with pharmaceutically acceptable adjuvants known to those of skill in the art of pharmaceutical formulations. The resultant dosage form is suitable for oral ingestions as, for example, a pill or capsule.

In yet another embodiment, the present invention provides a method for enhancing the oral availability of therapeutic polypeptides of the general formula formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally, wherein the method comprises the step of chemically linking the polypeptide to a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl to form a prodrug. Preferably, this embodiment of the present invention provides a prodrug where the polypeptide is chemically linked to the carrier moiety through a non-therapeutic linker species. More preferably, the linker species is an amino acid.

Known therapeutically active polypeptide species that have been demonstrated to be pharmacologically ineffective when delivered through typical

oral routes of administration can be modified through linkage to a carrier species to achieve effective bioavailability of the active entity.

In an alternative embodiment, the invention of the instant application encompasses a method for the treatment of a physiological condition through the oral administration of a therapeutically effective species comprising the steps of chemically linking a therapeutic polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variatbn thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally, to a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5 trimethoxycinnamoyl to form a prodrug, and orally administering the prodrug to a patient exhibiting the physiological condition. Preferably, in the practice of the method of the present invention, the polypeptide is chemically linked to the carrier moiety through a non-therapeutic linker species. More preferably still, the linker species is an amino acid.

Thus, utilizing the present invention, it is possible to treat physiological conditions through oral administration of therapeutically active polypeptides that would normally have to be administered through considerably less desirable routes of administration, such as by injection.

In still another embodiment, the invention of the instant application provides for a method for the controlled release administration of a

therapeutically effective polypeptide of the general formula aa_n, where *aa* is an amino acid, or a chemical or structural variation thereof, where *n* is an integer from 2 to 10, and wherein the polypeptide is poorly absorbed orally, comprising the steps of chemically linking the polypeptide to a carrier moiety selected from the group comprising cinnamoyl, benzoyl, phenylacetyl, 3,4 methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl to form a prodrug, and orally administering the prodrug to a patient. In a preferred embodiment, the polypeptide is chemically linked to the carrier moiety through a nontherapeutic linker species, and, more preferably still, the linker species is an amino acid. Due to the kinetics of the hepatic degradation of the prodrug of the present invention, the therapeutically active polypeptide species is released to the patient's system over relatively long periods of time, dosage dependent, to a maximum of nearly twenty-four hours.

EXAMPLE

Met-Enkephalin (Tyr-Gly-Gly-Phe-Met) is a naturally occurring pentapeptide (*n* = 5) belonging to the endorphin class. It is known to produce analgesia when given parenterally but no effect has been observed when given orally. Its mechanism of action relates to the binding to opioid delta receptors. Met-Enkephalin is very rapidly degraded *in vivo* into a tetra-peptide which is subsequently metabolized. The plasma levels of Met-Enkephalin, as well of those of the metabolites, are hardly measurable, even when administered parenterally. Its pharmacological activity is classically demonstrated in the hot

plate test with rats when administered parenterally. However, when administered orally Met-Enkephalin is unable to demonstrate any analgesic effect as expected.

According to the present invention, a prodrug Cinnamoyl-Met-Enkephalin (cinnamoyl-Tyr-Gly-Gly-Phe-Met), of the general form carrier-aa$_5$, demonstrated unexpectedly a strong, long-lasting analgesia in the hot plate test in rats when administered orally. Moreover, after 3 hours, but not after 7 hours, plasma levels of the tetra-peptide could be measured.

These results indicate that using a carrier such as disclosed herein, permits effective oral absorption of peptides of at least 5 amino acids in length as demonstrated by a long lasting pharmacological effect and by detectable plasma levels. Without carrier no pharmacological effect could be demonstrated nor any plasma level measured.